The impact of systemic chemotherapy on testicular FDG activity in young men with Hodgkin's lymphoma

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Abstract

Purpose Based on prior reports suggesting a positive correlation between fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET)/CT and total sperm count and concentration, we sought to identify changes in testicular FDG uptake over the course of chemotherapy in young men with Hodgkin's lymphoma.

Methods Fifty-two patients with a mean age of 24.2 years (range 15.5–44.4) at diagnosis monitored with FDG PET/CT to assess treatment response for Hodgkin's lymphoma were selected for this retrospective analysis under an Institutional Review Board waiver. Of the patients, 26 were treated with a chemotherapy regimen known to cause prolonged and sometimes permanent azoospermia (BEACOPP—bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone) and 26 with a regimen known to have a much milder effect on gonadal function (ABVD—doxorubicin,

bleomycin, vincristine, and dacarbazine). Each patient underwent one FDG PET/CT before treatment and at least one FDG PET/CT after start of chemotherapy. In all examinations, FDG activity was measured in the testes with different quantification metrics: maximum standardized uptake value (SUV_{max}), SUV_{mean} , functional volume (FV) and total testicular glycolysis (TTG), and blood pool activity determined (SUV_{mean}).

Results Testicular FDG uptake (SUV_{max}) was significantly associated with blood pool activity ($p < 0.001$). Furthermore, testicular FDG uptake metrics incorporating volume (e.g., FV and TTG) were associated with age. There was no significant change in SUV_{max} , SUV_{mean} , FV, and TTG from the PET/CT at baseline to the PET/CTs over the course of chemotherapy either for patients treated with BEACOPP or for patients treated with ABVD.

Conclusion For patients undergoing chemotherapy for Hodgkin's lymphoma, there is a significant association between testicular FDG uptake and blood pool activity, but no significant changes in FDG uptake over the course of chemotherapy. Therefore, FDG uptake may not be a feasible surrogate marker for fertility monitoring in patients with Hodgkin's lymphoma undergoing chemotherapy.

Keywords Fertility · Chemotherapy · Lymphoma · BEACOPP · ABVD · FDG · PET/CT

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Introduction

The improved outcomes achieved with current oncologic treatments have resulted in increasing interest in the identification and management of long-term adverse effects of cancer therapies. One such adverse effect is impaired fertility [1, 2]. Fertility is an important issue for patients with

Hodgkin's lymphoma, as this disease tends to affect younger individuals compared to other cancers (e.g., median age of patients diagnosed with Hodgkin's lymphoma is 38 years vs mean age at diagnosis of 67 years for prostate cancer) [3]. The effects of the common chemotherapeutic regimens used to treat Hodgkin's lymphoma on gonadal function have been well studied and are widely variable [4–8]. Treatment combinations including cyclophosphamide, vincristine, procarbazine, and prednisolone (COPP) have been found to substantially reduce fertility with post-treatment azoospermia in over 90 % of patients and permanent azoospermia in up to 30 % of patients treated with this regimen [9]. In a sperm analysis after baseline or escalated regimens with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone (BEACOPP) there was azoospermia in 93 and 87 %, respectively. The authors concluded that 8 cycles of BEACOPP chemotherapy led to temporary sterility in most male patients [10]. Other chemotherapy regimens have a much milder effect on gonadal function. For example, the doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD) regimen has been associated with a high rate of complete recovery of sperm count, with only mildly reduced fertility in up to 50 % of the patients [8].

^{18}F -Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is a commonly used imaging modality for staging, response assessment, and disease monitoring of patients with lymphoma [11–14]. On ^{18}F -FDG PET/CT, the normal testes demonstrate variable physiologic FDG uptake which demonstrates a positive correlation with age in children and teenage boys, and a physiologic decline after the age of 50 [15–18]. A recent study analyzed FDG PET/CT images in 20 consecutive cancer patients and found a positive correlation between FDG uptake in the testis and sperm quality indicated by total sperm count, sperm concentration, and sperm motility [19]. The authors suggested that FDG PET/CT could become a useful new tool in assisted reproductive technologies and other urologic applications to assess fertility, as a potential new application of ^{18}F -FDG PET/CT, in addition to the established roles in staging and follow-up. We therefore hypothesized that a significant decrease in testicular FDG uptake over the course of chemotherapy in patients treated with BEACOPP and little or no change in testicular FDG uptake in patients treated with ABVD could serve as surrogate markers for the impact on fertility.

Thus, the purpose of this study was to evaluate the changes in FDG uptake over the course of treatment in patients with Hodgkin's lymphoma receiving two different chemotherapeutic regimens with different effect on gonadal function (BEACOPP and ABVD).

Materials and methods

Patients

All patients with newly diagnosed Hodgkin's lymphoma between January 2000 and June 2011 were retrospectively screened under a waiver for informed consent requirement from the Institutional Review Board. Inclusion criteria were: (1) male, (2) age 15–50, (3) treatment with BEACOPP or ABVD chemotherapy regimens, and (4) ^{18}F -FDG PET/CT performed within 1 month prior to the start of chemotherapy and at least one ^{18}F -FDG PET/CT performed more than 1 month after the start of chemotherapy. Exclusion criteria were: (1) history of primary cancer other than Hodgkin's lymphoma and (2) previous treatment with pelvic radiation (the germinal epithelium is markedly sensitive to radiation).

A total of 99 patients were identified (26 patients treated with BEACOPP and 73 patients treated with ABVD). At our institution, BEACOPP is usually utilized for advanced stage and high-risk patients with an International Prognostic Score (IPS) ≤ 3 ; however, it is poorly tolerated by older adults. ABVD is given to patients with both early and advanced stage disease. In an attempt to reduce the confounding influence of age, for this study we selected all patients treated with BEACOPP ($n=26$) and the youngest 26 patients treated with ABVD, for a total of 52 patients in our study population.

Image acquisition and data analysis

All patients underwent PET/CT on a Discovery STE or LS or Discovery 690 (GE Medical Systems, Milwaukee, WI, USA) or a Biograph 16 (Siemens Medical Solutions, Hoffman Estates, IL, USA). A clinical imaging protocol was applied with an injection of 12–15 mCi FDG after at least 6 h of fasting. Approximately 60 min later, a low-dose, attenuation correction CT scan (120–140 kV, approximately 80 mA) was acquired, followed by acquisition of PET emission images from the pelvis to the skull base.

One reader trained in radiology and nuclear medicine, blinded for the used chemotherapy regimen measured the FDG activity in both testes [maximum and mean standardized uptake value (SUV_{max} , SUV_{mean}] as well as the testicular functional volume (FV) including all voxels with an SUV above 42 % of SUV_{max} and the overall testicular glucose activity (total testicular glycolysis—TTG), quantified as the product of the FV with the mean FDG activity in the same volume (Eq. 1).

$$\text{TTG} = \text{SUV}_{\text{mean}} \times \text{FV} \quad (1)$$

The mean FDG activity in the blood pool was measured using a standardized cubical volume of interest (VOI), with

a length of 3 cm and a diameter of 0.5 cm, placed in the center of the descending aorta.

Scans were divided into three categories: pre-chemotherapy (Scan A), during chemotherapy (Scan B_{1–n}, including all scans performed at least 1 month after chemotherapy start and within 1 month after chemotherapy stop), and post-chemotherapy (Scan C_{1–n}, including all scans at least 1 month after chemotherapy stop). For each patient, the relative and the absolute change in FDG quantification metrics (SUV_{max}, SUV_{mean}, FV, and TTG) between Scan A and all Scans B₁ to Scan B_n were calculated (Eqs. 2 and 3):

$$\text{Absolute change} = \text{Scan B}_{1-n} - \text{Scan A} \quad (2)$$

$$\text{Relative change} = (\text{Scan B}_{1-n} - \text{Scan A}) / \text{Scan A} \quad (3)$$

To assess the FDG uptake after chemotherapy we also calculated the relative and the absolute change between Scan B and all C Scans for each patient (Eqs. 4 and 5):

$$\text{Absolute change} = \text{Scan C}_{1-n} - \text{Scan B} \quad (4)$$

$$\text{Relative change} = (\text{Scan C}_{1-n} - \text{Scan B}) / \text{Scan B} \quad (5)$$

Statistical analysis

Generalized estimating equation analysis was used to test the association between SUV_{max}, SUV_{mean}, FV, and TTG and the chemotherapy regimen. We adjusted for the correlation between multiple observations within the same patient using an exchangeable correlation matrix. Additionally, the Wilcoxon rank sum test was used to assess differences between chemotherapy regimen and patient characteristics, including age at diagnosis, weight, and clinical stage. We used the Spearman rank correlation to assess relationship between blood pool measurements and FDG uptake measurements. All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient population

The 26 men with Hodgkin's disease treated with BEACOPP chemotherapy had a mean age of 22.7 years (range 15.5–44.4 years, median=18.7 years). The mean age of the 26 men treated with ABVD was 25.8 years (range 17.7–33.8 years, median=26.1 years). Most patients treated with

BEACOPP had stage IV disease, whereas the majority of patients treated with ABVD had stage II disease. All patients underwent one pre-chemotherapy (baseline) PET/CT. On average, each patient underwent 1.6 PET/CTs during chemotherapy (B Scans) and 3.8 PET/CTs after the completion of chemotherapy (C Scans). Summaries of patient demographics and PET/CT acquisition parameters are shown in Tables 1 and 2.

Testicular FDG uptake on pre-chemotherapy (baseline) PET/CTs (A Scans)

There was no significant difference in SUV_{max} and SUV_{mean} between patients treated with BEACOPP and those treated with ABVD ($p=0.34$ and $p=0.44$, respectively). The FV and TTG were significantly lower in patients treated with BEACOPP than in those treated with ABVD ($p=0.0087$). This corresponded to the younger age in group 1 treated with BEACOPP. Overall, the mean FV for patients younger than 19 years was 38.5 ml (range 16.9–89.1 ml) and 46.71 ml (range 13.5–125.3 ml) for patients older than 19 years. The FDG quantification metrics for testicular activity (SUV_{max}, SUV_{mean}, and TTG) showed significant correlation with the mean blood pool activity ($p<0.001$) (Table 3, Fig. 1).

Changes in FDG uptake from baseline (A Scans) to during (B Scans) and after (C Scans) chemotherapy

There was no significant difference between patients treated with BEACOPP versus patients treated with ABVD in the relative or absolute change between baseline scans and scans during chemotherapy or between the last scan under chemotherapy to the scans after treatment (Table 4). Also, when taking the time interval between the start of chemotherapy and the B Scans into account, there was no significant decrease in FDG uptake over the course of chemotherapy (Fig. 2). Also, for scans after

Table 1 Patient demographics

Patient information	Total (n=52)	BEACOPP (n=26)	ABVD (n=26)	p value
Age (years)	24.2±6.7	22.7±8.5	25.8±4.0	0.003
Weight (kg)	74.9±20.4	71.4±19.1	83.2±20.9	0.047
Stage				
I	3	1	2	
II	18	6	12	
III	12	6	6	
IV	19	13	6	

Table 2 Scan information

Scan parameters	Total (<i>n</i> =280)	BEACOPP (<i>n</i> =196)	ABVD (<i>n</i> =84)
FDG dose (mCi)	13.5±1.5	13.7±1.5	13.1±1.6
Uptake time (min)	71.6±15.8	72.6±17.1	69.4±12.0
Number of scans			
Pre-chemotherapy	52	26	26
During chemotherapy	90	58	32
After chemotherapy	138	112	26
Total scan number	280	196	84

chemotherapy there was no increase for the absolute or relative change when compared to the last scan under treatment (Fig. 3).

Discussion

Based on prior reports suggesting a positive correlation between FDG uptake on PET/CT and total sperm count and concentration, we sought to identify changes in testicular FDG uptake over the course of treatment in young men with Hodgkin's lymphoma. The impact of existing chemotherapeutic regimens on fertility has been well documented in numerous studies [4–7, 9]. We analyzed testicular FDG uptake over the course of BEACOPP, a chemotherapy regimen which is known to cause prolonged and sometimes permanent azoospermia [10], and compared it to the FDG uptake in patients treated with ABVD, which has been associated with mild or no azoospermia after the standard treatment regimen [20]. Based on these findings, we hypothesized that there would be a significant decrease in testicular FDG uptake over the course of chemotherapy in patients treated with BEACOPP and little or no change in testicular FDG uptake in patients treated with ABVD. We found that testicular FDG uptake was significantly associated with blood pool activity and also identified a positive association between FDG uptake metrics incorporating volume (e.g., TTG) and age under 19 years. There was no significant relative or absolute change for the FDG uptake metrics (SUV_{max} , SUV_{mean} , FV, and TTG) from the PET/CT at baseline to the PET/CTs during or after treatment either

for patients treated with BEACOPP or for patients treated with ABVD.

The previously published correlation between semen analysis and FDG uptake in the testis was shown in 20 patients with a similar age range to our study (mean age 22 years, range 14–35 years), who were analyzed only prior to chemotherapy for Hodgkin's lymphoma (15 patients) and other non-testicular malignancies. The FDG uptake metrics analyzed contained SUV_{mean} and a qualitatively drawn FV. The most consistent correlation with sperm quality parameters was achieved with the FV; however, qualitatively drawn volumes are prone to a high interobserver variability and could influence the results, especially in a small study population.

The correlation between testicular FDG uptake and blood pool activity observed for both therapy groups and all scans before, during, or after chemotherapy ($p<0.0001$) probably reflects the observation that testes are well-perfused organs [21]. Blood pool activity depends on a number of factors, including blood glucose, uptake time, and injected dose [22], and this might partly explain the high variability in testicular FDG uptake observed in our study and in other studies [17, 18]. When comparing patients treated with BEACOPP and those treated with ABVD, the only significant difference in FDG uptake metrics was a lower TTG and FV for the BEACOPP group. This finding was observed in all PET/CTs, including those pre-chemotherapy examinations and probably results from the fact that, despite our attempts to reduce the bias related to patient age by including the 26 youngest patients treated with ABVD, patients treated with BEACOPP were still significantly younger (11 patients younger than 19 years, compared to 1 patient

Table 3 Correlation between testicular FDG uptake and mean blood pool activity

Variable	BEACOPP (<i>n</i> =26)	<i>p</i> value	ABVD (<i>n</i> =26)	<i>p</i> value
SUV_{max}	3.30±0.85	<0.0001	3.51±0.93	<0.0001
SUV_{mean}	2.07±0.52	<0.0001	2.19±0.56	<0.0001
TTG	764.91±288.34	<0.0001	1207.30±483.61	<0.0001
FV	376.78±125.88	0.017	550.71±193.71	0.018

Fig. 1 The correlation between testicular FDG activity and FDG blood pool activity for all scans (Scan A, Scan B, and Scan C) was statistically significant for both chemotherapy regimens **a** BEACOPP ($p<0.0001$) and **b** ABVD ($p<0.0001$)

younger than 19 years in the ABVD group). The association between age and testicular volume is well known[23], and thus it is expected that younger patients would have lower FDG uptake metrics that incorporate volume, such as TTG or FV.

Our study had some limitations. First, we had a relatively small sample size. Second, the retrospective nature of the study led to a high variability in time intervals between FDG PET/CT scans, both during and after chemotherapy. Ideally, the scan time points would have been standardized to truly compare the same amount and duration of drug affecting the testicles in each patient. The retrospective design also meant that we could not control for the potential bias associated with treatment selection or the demographic characteristics of patients in the two chemotherapy regimens evaluated, even though we attempted to reduce the confounding effect of age by including the youngest patients receiving ABVD.

Third, semen analysis was not available as this is not routinely performed in all patients undergoing chemotherapy for Hodgkin's lymphoma at our institution; therefore, we cannot make any assumptions regarding the correlation of FDG uptake and sperm count, concentration, or quality. The fact that we found no significant difference in FDG uptake between patients treated with BEACOPP and ABVD chemotherapy, however, leads us to suspect that, even if there was a significant difference in sperm parameters between the two groups, this would not have been detected through testicular FDG uptake measurements.

Conclusion

For patients undergoing chemotherapy for Hodgkin's lymphoma, we identified a significant association between

Table 4 Relative and absolute changes for each patient between Scan A and Scan B_n (during chemotherapy) and Scan B and Scan C_n (after chemotherapy)

Variable	Time point	Total (n=52)	BEACOPP (n=26)	ABVD (n=26)	Chi-square (generalized linear model)	p value (generalized linear model)
SUV _{max} absolute difference	During chemotherapy	0.14±0.90	0.27±0.89	-0.11±0.87	2.08	0.1496
	After chemotherapy	-0.30±0.80	-0.36±0.82	0.00±0.58	1.36	0.2428
SUV _{mean} absolute difference	During chemotherapy	0.08±0.50	0.15±0.50	-0.05±0.47	2.53	0.1114
	After chemotherapy	-0.19±0.49	-0.24±0.51	0.01±0.32	2.06	0.1514
FV total absolute difference	During chemotherapy	-68.67±146.88	-95.39±130.11	-20.95±164.83	2.49	0.1148
	After chemotherapy	44.16±132.82	44.84±120.60	39.72±200.14	0.21	0.6501
TTG total absolute difference	During chemotherapy	-127.46±274.22	-157.84±262.22	-73.20±291.37	0.86	0.3539
	After chemotherapy	19.86±289.44	4.77±245.96	117.94±487.19	0.96	0.3273
SUV _{max} relative difference	During chemotherapy	8±30 %	11±33 %	2±24 %	1.33	0.2489
	After chemotherapy	-6±22 %	-8±23 %	1±18 %	1.20	0.2734
SUV _{mean} relative difference	During chemotherapy	6±25 %	9±26 %	1±22 %	1.83	0.1764
	After chemotherapy	-6±21 %	-8±22 %	-2±15 %	0.46	0.1801
FV total relative difference	During chemotherapy	-12±27 %	-17±23 %	-4±32 %	2.38	0.1227
	After chemotherapy	20±47 %	20±46 %	16±55 %	0.33	0.5648
TTG total relative difference	During chemotherapy	-11±24 %	-12±24 %	-9±25 %	0.12	0.7313
	After chemotherapy	10±45 %	8±43 %	19±58 %	1.04	0.3086

Fig. 2 The absolute or relative change for SUV_{max} or TTG values did not show any significant trend during chemotherapy (a and b). Illustrated are all the scans during chemotherapy over the course of treatment, with the absolute difference to the scan prior to chemotherapy for SUV_{max} and TTG (c and d). Also, the relative difference between the scans before and during chemotherapy did not show any difference between the two chemotherapy regimens. Group 1 (BEACOPP): red, group 2 (ABVD): black

Fig. 3 The absolute or relative change for SUV_{max} or TTG values did not show any significant trend over time after chemotherapy (a and b). Illustrated are all the scans after chemotherapy over the course of follow-up, with the absolute difference to the last scan during chemotherapy for SUV_{max} and TTG (c and d). Also, the relative difference between the scans after chemotherapy and the last scan during chemotherapy did not show any difference between the two chemotherapy regimens. Group 1 (BEACOPP): red, group 2 (ABVD): black

testicular FDG uptake and blood pool activity, but no significant changes in FDG uptake over the course of chemotherapy with two common regimens with well-established effects on fertility. We conclude that FDG uptake is not a feasible surrogate marker for fertility monitoring in patients with Hodgkin's lymphoma undergoing chemotherapy.

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Conflicts of interest None.

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